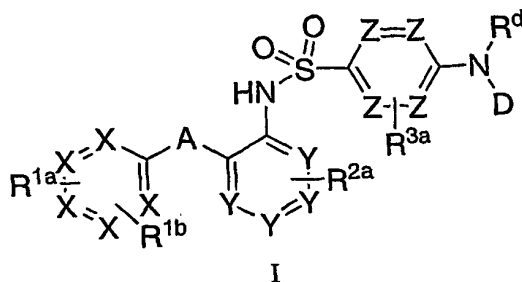


WHAT IS CLAIMED IS:

1. A compound of formula I and pharmaceutically acceptable salts thereof:



wherein

A is O, CO, S, NR^d, or CR^bR^c;

D is COR⁴, C(O)NR^dR⁴, C(O)OR⁴, SO₂R^{4'}, SO₂NR^dR⁴;

- 10 X, Y and Z are independently a ring carbon atom or a ring nitrogen atom, with the proviso that 0-3 X, 0-3 Y and 0-3 Z are ring nitrogen atoms;

R^{1a} and R^{1b} are independently selected from (1) H, (2) halogen, (3) C₁₋₆alkyl optionally substituted with 1-5 groups independently selected from halogen, nitro, cyano, COR^a, CO₂R^a, C(O)NR^dR^e, OR^a, OC(O)R^a, SR^a, SO₂R^f, S(O)R^f, NR^dR^e, NR^dC(O)R^a and NR^dSO₂R^f, (4) C(O)R^a, (5) CO₂R^a, (6)

- 15 C(O)NR^dR^e, (7) OR^a, (8) OC(O)R^a, (9) OC(O)NR^dR^e, (10) NR^dR^e, (11) NR^dC(O)R^a, (12) NR^dC(O)OR^a, (13) NR^dC(O)NR^dR^e, (14) NR^dSO₂R^f, (15) SR^a, (16) S(O)R^f, (17) SO₂R^f, (18) SO₂NR^dR^e, (19) CN, (20) NO₂, (21) optionally substituted aryl, (22) optionally substituted heteroaryl, (23) optionally substituted heterocyclyl, (24) optionally substituted aryl-C₁₋₆alkyl, (25) optionally substituted heteroaryl-C₁₋₆alkyl, and (26) optionally substituted heterocyclyl-C₁₋₆alkyl; wherein the

- 20 substituents for aryl, heteroaryl, heterocyclyl, alkyl, heteroalkyl and heterocyclylalkyl are 1 to 3 groups independently selected from halogen, cyano, nitro, OR^a, NR^dR^e, NR^dC(O)R^a, NR^dSO₂R^f, OC(O)R^a, NR^dC(O)₂R^a, SR^a, SO₂R^f, oxo (for heterocyclyl and heterocyclylalkyl), C(O)R^a, C(O)₂R^a, C₁₋₄ alkyloxy, aryl, aryl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, or

- 25 R^{1a}, R^{1b} and adjacent carbon atoms to which they are attached together form a saturated, partially unsaturated or aromatic 5- or 6-membered ring containing 0 to 2 heteroatoms selected from N, N-R^g, O and S;

R^{2a} and R^{3a} are independently selected from (1) H, (2) halogen, (3) OR^a, (4) NR^dR^e, (5) CN, (6) NO₂, (7) CO₂R^a, (8) COR^a, and (9) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms,

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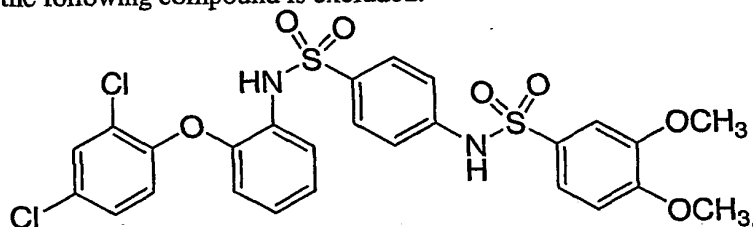
- R⁴ is selected from (1) H, (2) C₁₋₆alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, C₃₋₆cycloalkyl, COR^a, CO₂R^a, C(O)NR^dRe, OR^a, OC(O)R^a, SR^a, SO₂R^f, S(O)R^f, NR^dRe, NR^dC(O)R^a, NR^dSO₂R^f, and NR^dC(O)₂R^a, (3) optionally substituted C₃₋₆cycloalkyl, (4) COR^a, (5) COOR^a, (6) optionally substituted aryl, (7) optionally substituted heteroaryl, (8) optionally substituted heterocyclyl, (9) optionally substituted aryl-C₁₋₆alkyl, (10) optionally substituted heteroaryl-C₁₋₆alkyl, and (11) optionally substituted heterocyclyl-C₁₋₆alkyl; wherein the substituents for cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl and heterocyclylalkyl are 1 to 3 groups independently selected from halogen, cyano, nitro, OR^a, NR^dRe, NR^dC(O)R^a, NR^dSO₂R^f, OC(O)R^a, NR^dC(O)₂R^a, SR^a, SO₂R^f, oxo (for heterocyclyl and heterocyclylalkyl), C(O)R^a, C(O)₂R^a, C₁₋₄alkyloxy, aryl optionally substituted with 1 or 2 halogen atoms, aryl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;
- R^{4'} is a group selected from R⁴ except R^{4'} is not H;
- R^a is (1) H, (2) C₁₋₆ alkyl optionally substituted with 1 to 5 groups independently selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy and C₃₋₆ cycloalkyl, (3) C₃₋₆ cycloalkyl, (4) optionally substituted aryl, (5) optionally substituted heteroaryl, (6) optionally substituted heterocyclyl, (7) optionally substituted aryl-C₁₋₆alkyl, (8) optionally substituted heteroaryl-C₁₋₆alkyl, and (9) optionally substituted heterocyclyl-C₁₋₆alkyl; wherein the substituents for aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl and heterocyclylalkyl are 1 to 3 groups independently selected from halogen, cyano, nitro, OR^g, NR^dRe, NR^dC(O)R^g, NR^dSO₂R^f, OC(O)R^g, NR^dC(O)₂R^g, SR^g, SO₂R^f, oxo (for heterocyclyl and heterocyclylalkyl), C(O)R^g, C(O)₂R^g, C₁₋₄ alkyloxy, aryl, aryl-C₁₋₄alkyl, heteroaryl, heteroaryl-C₁₋₄alkyl, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;
- R^b and R^c are independently selected from H, halogen, or C₁₋₄alkyl optionally substituted with 1 to 5 halogen atoms;
- R^d and R^e are independently selected from (1) H, (2) C₁₋₄alkyl, optionally substituted with 1 to 5 groups independently selected from halogen, amino, mono-C₁₋₄alkylamino, di-C₁₋₄alkylamino, and SO₂R^f, (3) aryl-C₁₋₆alkyl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, (4) heteroaryl-C₁₋₆alkyl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, and (5) C₃₋₆ cycloalkyl, or
- R^d and R^e, or R^d and R⁴, or R^d and R^{4'}, together with the atom or atoms to which they are attached, complete a 4- to 8-membered saturated, partially saturated or aromatic ring optionally containing 1 to 3 heteroatoms independently selected from N, NR^g, O, S, and SO₂, and said ring being optionally fused to a benzene or a 5- or 6-membered heteraromatic ring, and optionally substituted with 1 to 3 substituents

independently selected from halogen, cyano, nitro, OR_g, oxo, C₃₋₆ cycloalkyl, aryl, aryl-C₁₋₄alkyl, heteroaryl, NR_gR_g, NR_gCOR_g, NR_gCO₂R_g and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;

R^f is selected from (1) C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms, (2) C₁₋₄ alkyloxy, and (3) aryl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C₁₋₄ alkyloxy, C₃₋₆ cycloalkyl and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms;

R_g is selected from (1) H, (2) C₁₋₄alkyl, (3) aryl, (4) aryl-C₁₋₆alkyl, (5) C(O)₂C₁₋₄alkyl and (6) C(O)C₁₋₄alkyl;

with the proviso that when each occurrence of X, Y and Z is a ring carbon atom, R^{1a} and R^{1b} are each hydrogen or chlorine, and R^{2a} and R^{2b} are each hydrogen, then D is not NHC(O)C₁₋₆alkyl; with the further proviso that the following compound is excluded:



2. A compound of Claim 1 wherein A is C(O) or O.

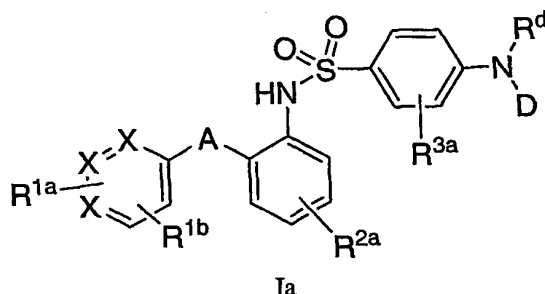
3. A compound of Claim 1 wherein D is COR⁴, C(O)NR^dR⁴ or C(O)OR⁴.

4. A compound of Claim 1 wherein each occurrence of Y and Z represents a ring carbon atom, and one X is a ring carbon or nitrogen atom and the others are ring carbon atoms.

5. A compound of Claim 3 wherein R⁴ is selected from (1) C₁₋₆alkyl substituted with 1 to 5 halogen atoms, OR^a, NR^dRe or C(O)NR^dRe in which, for these two occurrences, R^d and R^e together complete a 4- to 8-membered ring optionally containing an additional heteroatom selected from NR_g, O, S, and SO₂, and said ring being optionally fused to a benzene or a 5- or 6-membered heteraromatic ring, and optionally substituted with 1 to 3 substituents independently selected from halogen, cyano, nitro, OR_g, oxo, C₃₋₆ cycloalkyl, aryl, heteroaryl, NR_gR_g, NR_gCOR_g, NR_gCO₂R_g and C₁₋₄ alkyl optionally substituted with 1 to 5 halogen atoms; (2) optionally substituted heteroaryl; (3) optionally substituted heteroaryl-C₁₋₄alkyl; (4) optionally substituted heterocyclyl; (4) optionally substituted heterocyclyl-C₁₋₄alkyl; wherein the substituents for heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl are 1 to 3 groups independently selected from halogen, cyano, nitro, OR^a, NR^dRe,

$\text{NR}^d\text{C}(\text{O})\text{R}^a$, $\text{NR}^d\text{SO}_2\text{R}^f$, $\text{OC}(\text{O})\text{R}^a$, $\text{NR}^d\text{C}(\text{O})_2\text{R}^a$, SR^a , SO_2R^f , oxo (for heterocyclyl and heterocyclylalkyl), $\text{C}(\text{O})\text{R}^a$, $\text{C}(\text{O})_2\text{R}^a$, C_{1-4} alkyloxy, aryl, aryl- C_{1-4} alkyl, heteroaryl, heteroaryl- C_{1-4} alkyl, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms.

- 5
6. A compound of Claim 1 having the formula Ia and pharmaceutically acceptable salts thereof:



wherein

- 10 A is O or $\text{C}(\text{O})$;
one of X is a ring carbon or nitrogen atom, and the others are ring carbon atoms;
D is $\text{C}(\text{O})\text{R}^4$, $\text{C}(\text{O})\text{NR}^d\text{R}^4$ or $\text{C}(\text{O})\text{OR}^4$;
R1a and R1b are independently selected from hydrogen, halogen, C_{1-4} alkyl, cyano, SR^a , OR^a and CF_3 ;
R2a and R3a are independently H or halogen;
15 R4, Ra and Rd are as defined in Claim 1.

7. A compound of Claim 6 wherein D is $\text{C}(\text{O})\text{R}^4$, and R4 is selected from (1) C_{1-4} alkyl substituted with one to 5 groups independently selected from halogen, C_{3-6} cycloalkyl, NR^dR^e , $\text{NR}^d\text{C}(\text{O})_2\text{R}^a$, $\text{C}(\text{O})\text{NR}^d\text{R}^e$, $\text{C}(\text{O})\text{OR}^a$, and OR^a ; (2) C_{3-6} cycloalkyl; (3) phenyl; (4) phenyl-
20 C_{1-4} alkyl; (5) optionally substituted heteroaryl; (6) optionally substituted heteroaryl- C_{1-4} alkyl; (7) optionally substituted heterocyclyl; and (8) optionally substituted heterocyclyl- C_{1-4} alkyl; wherein heteroaryl, including as part of heteroarylalkyl, is selected from benzofuranyl, pyrazolo[1,5-a]-pyrimidinyl, 1-azaindolizynyl, s-triazolo[1,5-a]pyrimidinyl, thieno[3,2-b]pyridinyl isoxazolyl, pyrazinyl, pyrazolyl, pyrimidinyl, benzisoxazolyl, pyridyl, indolyl, benzimidazolyl, benzthiazolyl and imidazo[2,1-
25 b]thiazolyl; heterocyclyl, including as part of heterocyclylalkyl, is selected from morpholinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl and imidazolidinyl; the substituents for heteroaryl is 1 or 2 groups independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, and OR^a ; and the substituents for heterocyclyl is 1 to 3 groups independently selected from oxo and C_{1-4} alkyl.

8. A compound of Claim 7 wherein R^4 is selected from (1) C_{1-4} alkyl substituted with NR^dRe or $C(O)NR^dRe$ where for both groups R^d and Re , together with the nitrogen atom to which they are attached, complete an optionally substituted 5- or 6-membered saturated ring having 0 to 1 additional ring heteroatom selected from NR^g , O, S and SO_2 , and wherein said substituent is 1 or 2 groups independently selected from OR^a , halogen, C_{1-4} alkyl and oxo; (2) optionally substituted heteroaryl wherein said heteroaryl is selected from pyrazolyl, isoxazolyl, pyrimidinyl, benzofuranyl, pyrazolo[1,5-a]pyrimidinyl, 1-azaindoliziny, s-triazolo[1,5-a]pyrimidinyl, imidazo[2,1-b]thiazolyl, thieno[3,2-b]pyridinyl, and said substituent is 1 to 3 groups independently selected from furanyl, pyridyl, benzyl, phenyl optionally substituted with halogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, trifluoromethyl, halogen, and C_{1-4} alkoxy.

9. A compound of Claim 6 wherein D is $C(O)NR^dR^4$, wherein R^d is H and R^4 is selected from (1) C_{1-4} alkyl substituted with a group selected from halogen, OR^a , CO_2R^a , $NHCOR^a$, NR^dRe and $C(O)NR^dRe$; (2) optionally substituted heteroaryl- C_{1-4} alkyl wherein heteroaryl is selected from azaindoliziny, imidazolyl, benzimidazolyl, pyrazinyl, pyridyl, indolyl, triazolyl, thiazolyl, imidazo[1,2-a]pyridyl, imidazo[1,2-a]pyrimidinyl, imidazo[2,1-b]thiazolyl, and pyrazolo[1,5-a]pyrimidinyl; (3) optionally substituted heterocyclyl- C_{1-4} alkyl wherein heterocyclyl is selected from tetrahydropyranyl, tetrahydrofuranyl and dioxanyl; (4) optionally substituted heterocyclyl selected from pyrrolidinyl and piperidinyl; (5) CO_2R^a ; (6) C_{3-6} cycloalkyl; and (7) optionally substituted phenyl- C_{1-4} alkyl; or R^d and R^4 together with the nitrogen atom to which they are attached complete an optionally substituted 5- or 6-membered saturated ring having 0 to 1 additional ring heteroatom selected from NR^g , O, S and SO_2 , wherein said ring is optionally fused to a benzene or a 5- or 6-membered heteroaryl ring, and said substituent is 1 or 2 groups independently selected from OR^a , halogen, C_{1-4} alkyl, NR^dRe , $NR^dCO_2R^a$, and oxo.

10. A compound of Claim 9 wherein R^d is H and R^4 is selected from (1) C_{1-4} alkyl substituted with NR^dRe or $C(O)NR^dRe$, wherein for both groups R^d and Re together with the nitrogen to which they are attached complete an optionally substituted 5- or 6-membered saturated ring having 0 to 1 additional ring heteroatom selected from NR^g , O, S and SO_2 , and wherein said substituent is 1 or 2 groups independently selected from OR^a , halogen, C_{1-4} alkyl and oxo; (2) heterocyclyl or heterocyclyl- C_{1-4} alkyl wherein said heterocyclyl is selected from pyrrolidinyl, 1,4-dioxanyl, and tetrahydropyranyl; and (3) heteroaryl- C_{1-4} alkyl optionally substituted with 1 to 3 C_{1-4} alkyl groups, wherein said heteroaryl is selected from imidazolyl, 1-azaindoliziny, imidazo[2,1-b]thiazolyl, and pyrimidinyl.

11. A compound of Claim 7 wherein D is C(O)OR⁴, and R⁴ is selected from (1) C₂₋₄alkyl substituted with NR^dR^e or C(O)NR^dR^e in which, for these two groups, R^d and R^e together with the nitrogen atom to which they are attached complete an optionally substituted 5- or 6-membered saturated ring having 0 to 1 additional ring heteroatom selected from NR^g, O, S and SO₂, and wherein said substituent is 1 or 2 groups independently selected from OR^a, halogen, C₁₋₄alkyl and oxo; (2) heterocyclyl-C₁₋₄alkyl optionally substituted with 1 to 3 groups independently selected from C₁₋₄alkyl and oxo, wherein heterocyclyl is selected from tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, morpholinyl, oxazolidinyl, dioxanyl, and dioxolanyl; (3) furanyl-C₁₋₄alkyl; and (4) phenyl-C₁₋₄alkyl.

12. A compound of Claims 6, 7, 8, 9, 10 or 11 wherein the aryl group C₃X₃(R_{1a})(R_{1b}) is selected from (1) phenyl optionally substituted with 1 or 2 halogen atoms; (2) 2-pyridyl; and (3) 5-fluoro-2-pyridyl.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable excipients.

14. Use of a compound of formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament useful in the treatment or prevention of diseases or disorders mediated through the bradykinin receptor pathway.

15. The use of Claim 14 wherein said disease or disorder is selected from neuropathic pain, acute pain and inflammatory pain.